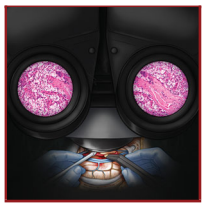

Neuropathology of Surgically Managed Epilepsy Specimens

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Epilepsy is characterized as recurrent seizures, and it is one of the most prevalent disorders of the human nervous system. A large and diverse profile of different syndromes and conditions can cause perturbations in neural networks that are associated with epilepsy. Advances in neuroimaging and electrophysiological monitoring have enhanced our ability to localize the neuropathological lesions that alter the neural networks giving rise to epilepsy, whereas advances in surgical management have resulted in excellent seizure control in many patients following resections. Histopathologic study using a variety of special stains, molecular analysis, and functional studies of these resected tissues has facilitated the neuropathological characterization of these lesions. Here, we review the neuropathology of common structural lesions that cause epilepsy and are amenable to neurosurgical resection, such as hippocampal sclerosis, focal cortical dysplasia, and its associated principal lesions, including long-term epilepsy-associated tumors, as well as other malformations of cortical development and Rasmussen encephalitis.

KEY WORDS: Epilepsy, Focal cortical dysplasia, Hippocampal sclerosis, Malformation of cortical development, Long-term epilepsy-associated tumor, Medically refractory, Neuropathology

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Epilepsy is a common condition that is characterized by recurrent seizures associated with diverse conditions. Medications and other treatments can sufficiently manage epilepsy in the majority of patients; however, as many as 30% will develop medically intractable epilepsy. A subset of these patients may be candidates for a neurosurgical approach to epilepsy management with a good chance of becoming seizure free.[1,2] To determine if an epilepsy patient is a surgical candidate, an extensive, multidisciplinary evaluation is required. Neurosurgical approaches that have the potential to cure epilepsy tend to be most effective when seizures arise from a localized structural alteration of neocortex or from certain subcortical sites. Surgical resection permits the neuropathological and molecular analysis of the excised lesions, which has enhanced our understanding of these epileptogenic lesions. Here, we illustrate the neuropathology of common epileptogenic lesions that are amenable to a neurosurgical approach, such as hippocampal sclerosis (HS), focal cortical dysplasia (FCD), and its associated principal lesions, long-term epilepsy-associated tumors (LEAT), as well as other malformations of cortical development (MCD), including hemimegalencephaly, tuberous sclerosis complex (TSC), polymicrogyria, and Rasmussen encephalitis.

ABBREVIATIONS: CA, cornu ammonis; **DNET,** dysembryoplastic neuroepithelial tumor; **FCD,** focal cortical dysplasia; **FLAIR,** fluid-attenuated inversion recovery; **GC,** granule cell; **HS,** hippocampal sclerosis; **ILAE,** International League Against Epilepsy; **LEAT,** long-term epilepsy-associated tumor; **MCD,** malformations of cortical development; **OLC,** oligodendroglial-like cell; **TSC,** tuberous sclerosis complex

HIPPOCAMPAL SCLEROSIS

HS can occur alone or in combination with other pathologies, which will be described. Under the current International League Against Epilepsy (ILAE) classification system, HS associated with cortical dyslamination within the temporal lobe is classified as FCD type IIIa. HS can be a secondary change induced by chronic seizures, particularly temporal lobe seizures,

in which it may represent a hypoxic/ischemic lesion because of high metabolic demand during prolonged seizures.

HS is the most common histopathological diagnosis in adult patients with drug-resistant epilepsy. In one of the largest series, HS was diagnosed in 36% of all specimens (44.5% of specimens from adults and 15% of children) and 54% of temporal lobe resections.[3] In some patients, HS coexists with a second lesion outside of the hippocampus or temporal lobe. These "dual pathology" lesions have been reported in 1.5%-5.1% of cases.[3,4] The second lesions are heterogeneous and include FCD, low-grade tumors, vascular lesions, ischemic injuries early in life, and glial scars.

Imaging features include decreased hippocampal volume, increased signal in T_2-weighted images, and disruption of hippocampal architecture.[5] The histologic correlate of hippocampal atrophy on magnetic resonance imaging (MRI) is severe loss of pyramidal neurons in various hippocampal sectors and the associated reactive gliosis correlates with increased T_2 signal.[6,7] The term mesial temporal sclerosis is appropriate if the amygdala and parahippocampal gyrus are involved.

Pathological examination of HS requires an en bloc resection specimen. By gross examination, the hippocampus may appear atrophic and the tissue may have a firm consistency because of reactive astrocytic gliosis ("sclerosis"). The severity of HS may vary along the length of the hippocampus, so multiple sections taken in the coronal plane should be examined.

HS is defined as neuronal cell loss in defined anatomic sectors of Ammon's horn (cornu ammonis [CA]). The dentate gyrus also commonly shows variable loss of granule cells (GC). Dispersion or widening of the GC layer to more than 10 neurons in thickness may be seen, and less frequently there is duplication or loss of the GC layer.

In 2013, the ILAE developed a consensus classification of HS subtypes to standardize diagnoses and facilitate clinicopathological, radiological, and electrophysiological correlations with postsurgical outcomes.[8] Currently, the ILAE classification system depends on semiquantitative analysis of neuronal loss by subfield with 4 currently recognized patterns. NeuN immunohistochemistry highlights neuronal loss making it helpful for subtype classification. The arborizing processes of reactive astrocytes are highlighted using GFAP immunostain. Occasionally temporal lobectomy specimens show only reactive gliosis without neuronal loss and these are not classified as HS.

Classical HS or ILAE type 1 HS is most common and diagnosed in approximately two-thirds of HS cases.[8] ILAE type 1 HS is defined by severe neuronal loss in the CA1 and CA4 regions, variable loss of neurons in CA3, and typically mild loss in CA2 (Figure 1A). A sharp border delineates neuronal loss in CA1 and preservation of the adjacent subiculum (Figure 1A). The dentate gyrus can also show variable degrees of GC loss and reduced GC density in the internal limb of the dentate gyrus, which is predictive of memory dysfunction (Figure 1B).[9,10] Abundant reactive astrocytes, highlighted by GFAP immunostain, are identified in areas of severe neuronal loss (Figure 1C and 1D). ILAE type 1 HS is often associated with an initial precipitating injury or febrile seizures in early childhood, early seizure onset, and good postsurgical seizure control.

ILAE type 2 HS is defined by loss of neurons and gliosis predominantly in CA1. Mild loss of neurons is occasionally seen in other subfields but may not be apparent without quantitative analysis. GC dispersion may be seen. ILAE type 2 HS is identified in approximately 5% to 10% of temporal lobe epilepsy resections. Some reports indicate poorer surgical outcomes with regard to long-term seizure control.[11] Importantly, loss of CA1 neurons should be interpreted in the clinical context and history of seizures. Severe neuronal loss and gliosis in CA1 is a pattern of injury also seen in hypoxic-ischemic injury and neurodegenerative conditions in older individuals without epilepsy.

ILAE type 3 HS is commonly referred to as end folium sclerosis, as neuronal loss and gliosis are predominantly restricted to CA4. ILAE type 3 is diagnosed in less than 10% of temporal lobe resections for epilepsy and thought to be more commonly associated with a second lesion, thereby fulfilling the criteria for dual pathology.

Temporal lobectomy is a well-established treatment of pharmacoresistant temporal lobe epilepsy; however, epilepsy may persist or recur after surgery. Long-term follow-up studies demonstrate approximately 60% of patients diagnosed with HS are seizure free at 1 yr and 50% of patients achieve seizure-free periods for up to 10 yr.[2,3] HS subtype classification helps predict surgical outcome, with ILAE type 1 HS having the best long-term seizure-free outcomes. Histopathological features may provide some additional prognostic information, although validation studies are needed.[12,13]

FOCAL CORTICAL DYSPLASIA

MCD are a diverse group of disorders that are due to poorly understood disturbances in development that result in neocortical dyslamination, manifesting as alterations in the expected hexalaminar arrangement.[14] A subset, known as FCD, is localized or focal in nature with limited cortical involvement. Collectively, FCD comprises the most common neuroanatomic lesion in children with medically refractory epilepsy.[15,16] Seizures are generally the primary clinical manifestation of FCD; unless the area of cortex involved is large, then focal neurological deficits may also occur. Rare cases of FCD are not associated with seizures and may mimic neoplasms. Semiology depends on the cortical site involved. Scalp electroencephalography characteristically reveals focal, rhythmic epileptiform discharges. Complete surgical removal of FCD is the best predictor of favorable outcome, so a thorough presurgical evaluation to include the full neuroanatomic and electrophysiological extent of the lesion is important.[17-19] Currently, FCD is classified based upon the recommendations of an ILAE committee, which recognizes 3 histopathological types I, II, and III.[20]

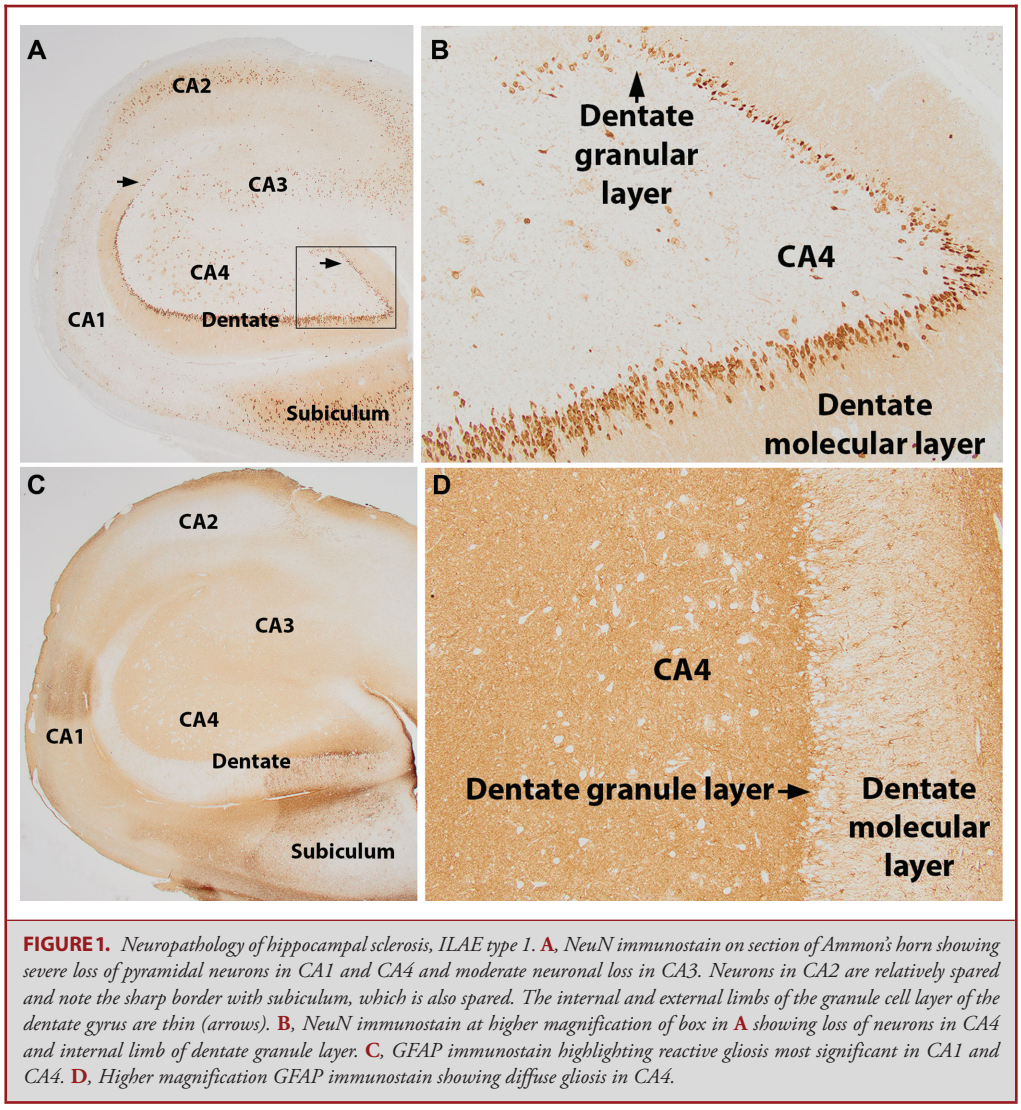

FIGURE 1. *Neuropathology of hippocampal sclerosis, ILAE type 1.* **A**, *NeuN immunostain on section of Ammon's horn showing severe loss of pyramidal neurons in CA1 and CA4 and moderate neuronal loss in CA3. Neurons in CA2 are relatively spared and note the sharp border with subiculum, which is also spared. The internal and external limbs of the granule cell layer of the dentate gyrus are thin (arrows).* **B**, *NeuN immunostain at higher magnification of box in* **A** *showing loss of neurons in CA4 and internal limb of dentate granule layer.* **C**, *GFAP immunostain highlighting reactive gliosis most significant in CA1 and CA4.* **D**, *Higher magnification GFAP immunostain showing diffuse gliosis in CA4.*

FCD Type I

FCD type I can occur in any lobe although it is thought to be more frequent in the temporal lobes.[21,22] The MRI may be normal (~37%) or there may be subtle changes such as an indistinct cortical white matter junction, increased white matter signal in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, or subcortical white matter volume loss.[19] FCD type I is a cortical malformation that results in altered layering of cortical neurons or dyslamination. Dyslamination can be due to either defects in radial migration and maturation of neurons in the case of type Ia or to alterations in neuron tangential migration as seen in type Ib. When both radial and tangential migration abnormalities coexist, it is designated as type Ic.[20]

Grossly cortex with FCD type Ia may appear normal or thicker than expected or show pale areas with indistinct cortical white matter junctions (Figure 2A). The characteristic histopathological feature of FCD type Ia is neuronal microcolumns where a linear array of neurons is oriented perpendicular to the cortical surface (Figure 2B and 2C). Such microcolumns contain more than 8 neurons, by definition, and they tend to occur in mid-cortex.[20] Neurons within microcolumns tend to be smaller than those located outside of microcolumns.[23] Microcolumns are reminiscent of the neuronal columns that occur during phases of neocortical development and may be found to a limited extent in normal or nonepileptic cortex.[24] NeuN immunostain can be very helpful in identifying inconspicuous microcolumns. NeuN may also reveal heterotopic white matter neurons that may be numerous although white matter neurons are also present in nonepileptic subjects and there is variability among cerebral lobes.[25,26]

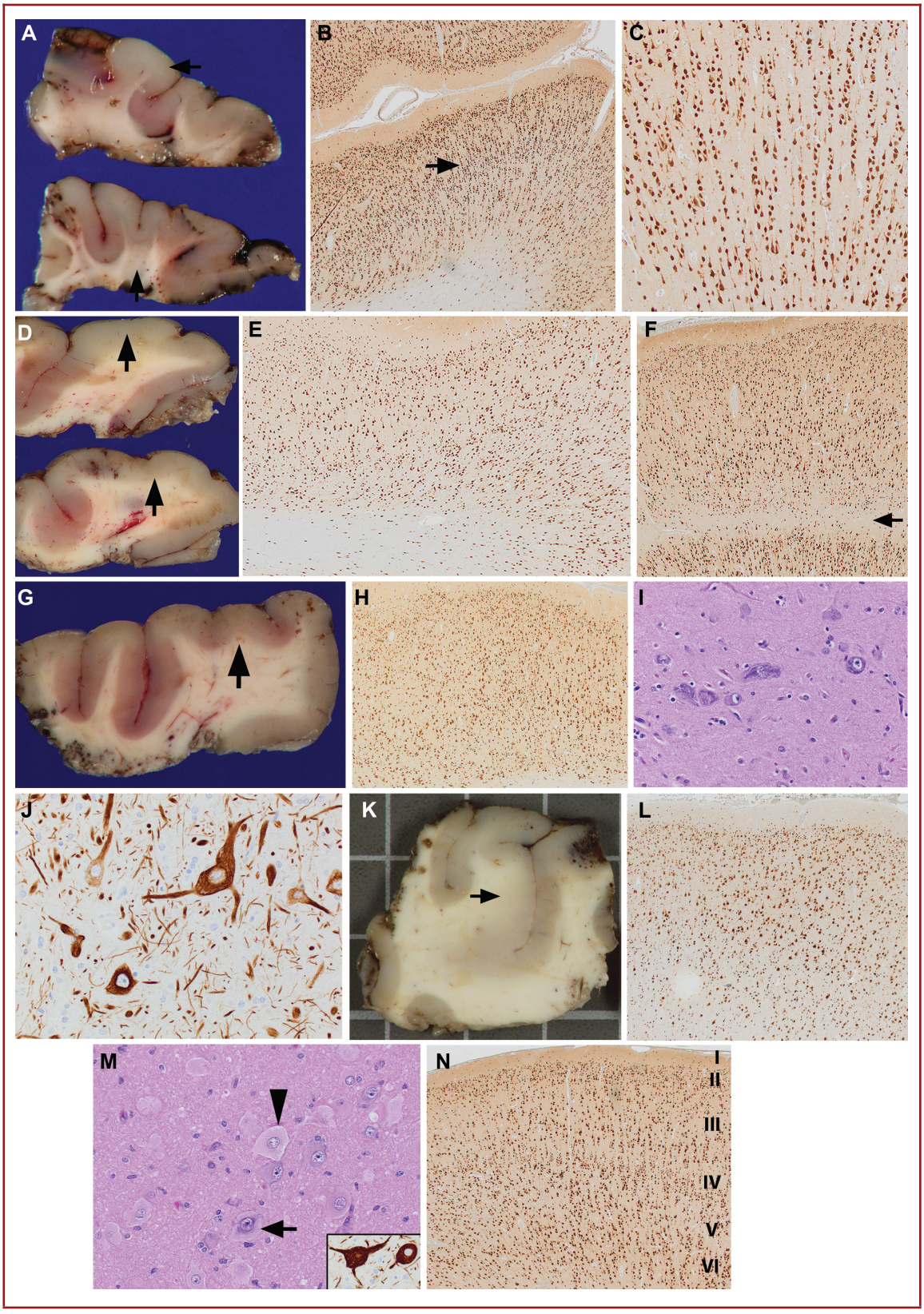

FIGURE 2. *Neuropathology of FCD type Ia* **A-C**, *Ib* **D-F**, *IIa* **G-J**, *and IIb* **K-M** *with normal NeuN-immunostained neocortex for comparison* **N**. **A**, *Sectioned gross resection specimen showing ill-defined cortical white matter junction and pale cortex (arrows) with FCD type Ia.* **B**, *Low and* **C**, *high magnification of NeuN immunostain showing microcolumns of neurons* **B** *(arrow) in mid-cortex.* **D**, *Sectioned gross resection specimen showing ill-defined cortical white matter junction and pale cortex (arrows) with FCD type Ib.* **E**, *NeuN immunostain showing indistinct cortical lamination.* **F**, *NeuN immunostain showing loss of neurons in layer IV (arrow) in another FCD type Ib case.* **G**, *Sectioned gross resection specimen showing odd sulcation pattern and pale cortex with ill-defined cortical white matter junction (arrow) of FCD type IIa.* **H**, *NeuN immunostain showing dyslamination.* **I**, *Hematoxylin and eosin-stained section showing a cluster of dysmorphic neurons with clumped Nissl substance.* **J**, *SMI32 immunostain reveals accumulation of neurofilament protein in the soma and distorted cell processes in dysmorphic neurons.* **K**, *Sectioned gross resection specimen showing ill-defined cortical white matter junction and pale cortex (arrow) involved with FCD type IIb.* **L**, *NeuN immunostain shows indistinct cortical layers.* **M**, *Hematoxylin and eosin-stained section reveals dysmorphic neurons (arrow) and balloon cells (arrowhead); inset shows SMI32 immunostain revealing neurofilament protein accumulation and bizarre processes of dysmorphic neurons.* **N**, *Normal cortex immunostained with NeuN with all 6 layers indicated for comparison purposes.*

Grossly cortex involved with FCD type Ib often appears thinner than expected with pale areas showing indistinct cortical white matter junctions (Figure 2D). Different manifestations of cortical dyslamination are possible in FCD type Ib. In some cases, all 6 layers, aside for the molecular layer, are unrecognizable in NeuN-immunostained sections, and the cortex is a jumble of haphazardly situated neurons (Figure 2E). Other times, one or more layers, such as layer II or IV, may be attenuated or missing and the edges of the layers appear ill defined (Figure 2F).[20] NeuN may also reveal heterotopic white matter neurons. FCD type Ic refers to lesions that exhibit mixed histopathological features of FCD type Ia and Ib as discussed.

FCD Type II

FCD type II can arise in any lobe, but seems to be more frequent in the frontal lobes.[21,22] FCD type II is easier to discern on MRI than FCD type I and only about 15% of patients will have a normal MRI.[17] Typical features include gyral and sulcal abnormalities, abnormal cortical thickness, indistinct cortical white matter junctions, and cortical and subcortical white matter signal hyperintensity in T2-weighted and FLAIR images.[19,27] The transmantle sign is characteristic, but only seen in about 30% of cases.[18,27,28]

Abnormal cellular differentiation in the form of dysmorphic neurons is the cardinal histopathological feature of FCD type IIa and IIb. Balloon cells, another manifestation of abnormal differentiation, are only seen in type IIb. Gross pathology of FCD type IIa may show an irregular sulcal pattern and thickened cortex with an indistinct cortical white matter junction (Figure 2G). Cortical dyslamination is pronounced, and often no layers aside from layer I are distinguishable (Figure 2H). FCD type IIa shows dysmorphic neurons, which vary in appearance, although characteristically, the nucleus and cell body are larger than expected (Figure 2I).[20] Dysmorphic neurons have irregularly distributed clumpy Nissl substance that may be peripherally displaced towards the cell membrane (Figure 2I). The processes of dysmorphic neurons are irregular and maloriented, and in immunostains, the cell bodies show accumulation of neurofilament proteins. Immunohistochemistry using antibodies that label phosphorylated and nonphosphorylated neurofilament proteins is useful to assess the presence of dysmorphic neurons because both accumulate in the cell body demonstrating a perinuclear network of neurofilaments (Figure 2J). Neurofilament immunohistochemistry is also helpful to highlight maloriented, irregular neuronal process of dysmorphic neurons. Dysmorphic neurons may occur anywhere in the cortex and even in the subcortical white matter.

The gross pathology of FCD type IIb may show an irregular sulcal pattern and pale thickened cortex with an indistinct cortical white matter junction (Figure 2K). There is characteristically marked cortical dyslamination so that only layer I is readily discernable (Figure 2L). FCD type IIb characteristically shows dysmorphic neurons and balloon cells and is reminiscent histopathologically of tubers in TSC (Figure 2M). Balloon cells typically have nuclei with open chromatin and visible nucleoli, and some are multinucleated. Balloon cells are large because of abundant glassy, eosinophilic cytoplasm that lacks Nissl substance. Balloon cells tend to occur in clusters of a few cells or singly. They may be located anywhere in the involved cortex or in white matter subjacent to FCD type IIb. Balloon cells express vimentin and phosphorylated-S6, and they may show variable expression of glial markers, such as GFAP, and neuronal markers, such as neurofilament (Figure 2M).[20,29] Stem cell markers, such as CD133, SOX2, or CD34, may be detected in balloon cells.[30,31] The cortical white matter junction is ill defined in FCD type IIb because of the presence of white matter neurons, dysmorphic neurons, and balloon cells as well as reduced white matter myelin, which can be appreciated in Luxol Fast Blue-stained sections.

A number of studies have reported somatic and germline genetic alterations associated with FCD, and some somatic alterations occur at low variant allele frequencies (<5%).[32,33] Somatic loss-of-function alterations in *SLC35A2*, an *N*-glycosylation pathway gene, has been identified in FCD type Ia and mild MCD.[32,34] Somatic gain-of-function alterations in mTOR pathway genes, *mTOR*, *AKT3*, *PIK3CA*, and *RHEB*, and germline or somatic loss-of-function alterations in negative regulators of the mTOR pathway, *DEPDC5*, *TSC1*, and *TSC2*, have been detected in FCD type II, tubers, and hemimegalencephly.[32,33] These data suggest that FCD variants form via genetically distinct pathogenetic processes with FCD type II and hemimegalencephaly representing somatic mTORopathies

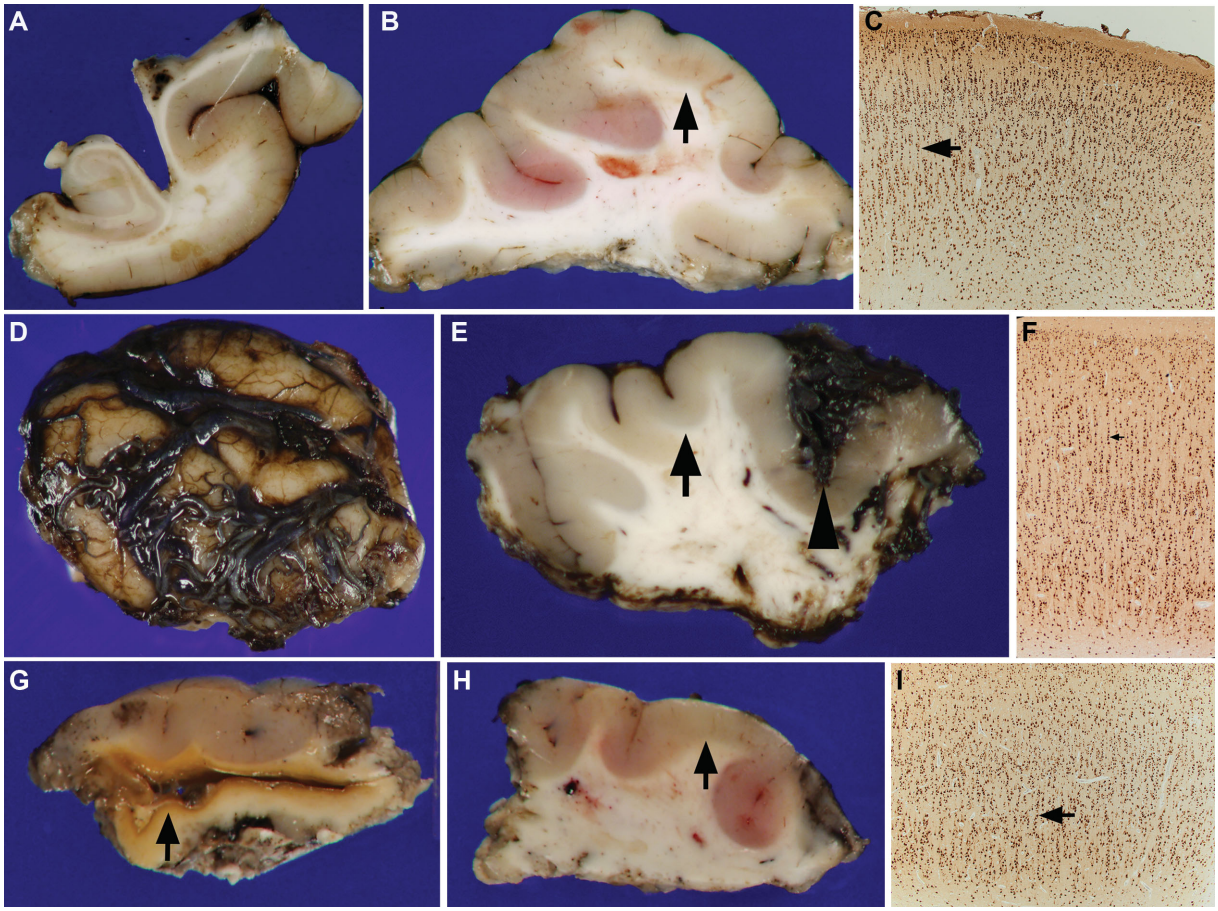

FIGURE 3. *Neuropathology of FCD types IIIa* **A-C**, *IIIc* **D-F**, *and IIId* **G-I** *and their principal lesions.* **A**, *Coronal sections through the hippocampus showing ill-defined sectors in Ammon's horn.* **B**, *Cut surface of cortical resection specimen showing pale cortex with ill-defined white matter junction (arrow).* **C**, *NeuN immunostain reveals microcolumns of neurons (arrow).* **D**, *External surface of a resection specimen with arteriovenous malformation.* **E**, *Cut surface showing superficial arteriovenous malformation (arrowhead) and small gyrus with a pale cortex (arrow).* **F**, *NeuN immunostain reveals microcolumns of neurons (arrow).* **G**, *Cut surface of a resection specimen from a patient who had perinatal hypoxic-ischemic injury resulting in a cystic cavity and glial scarring in white matter (arrow).* **H**, *Cut surface of a resection specimen showing pale cortical area (arrow) adjacent to the lesion in* **G**. **I**, *NeuN immunostain reveals microcolumns of neurons (arrow).*

(~60% of cases), whereas FCD type I and mild MCD are due to perturbations in glycosylation (~30% of cases).[32] Figure 2N shows normal cerebral cortex with the expected 6 layers of neurons for comparison purposes.

FCD Type III

FCD type III is diverse and denotes cortical dyslamination occurring next to or in the same lobe as a principal lesion.[20] There are 4 types, based on the nature of the principal lesion: type IIIa is associated with HS, type IIIb is associated with a neoplasm, type IIIc is associated with a variety of vascular lesions, and type IIId is associated with various lesions acquired in early life. FCD type III group is broad and is in need of better characterization in terms of clinical, electropathophysiological, neuroimaging, and neuropathological features, which will likely inform future classification systems.

FCD Type IIIa

In FCD type IIIa, temporal cortical dyslamination is accompanied by ipsilateral HS (Figure 3A-3C). HS is characterized by neuronal loss and gliosis in Ammon's horn, as previously mentioned, and this overlaps with the related condition, mesial temporal sclerosis, which also shows involvement of amygdala and entorhinal cortex, so mesial temporal sclerosis should not be included as FCD type IIIa.[20]

Seizures arise from the hippocampus/amygdala 40% of the time, whereas 35% come from temporal neocortex and 22% come from both locations.[35-37] The pathogenesis of type IIIa is

unclear. It is possible that the dysplastic neocortex is acquired secondary to HS or vice versa or, less likely, the cortical and hippocampal pathologies each arose by distinct mechanisms. Data indicate that the cortical dysplasia and HS share a common pathogenesis because patients with FCD type IIIa and isolated HS share common clinical features and outcomes.[21,38,39]

FCD Type IIIb

In FCD type IIIb, cortical dyslamination resides adjacent to a neoplasm. Certain neoplasms known as LEAT are common in this setting although the prevalence rate at which tumor and FCD coexist varies.[20,40-42] Ganglioglioma and dysembryoplastic neuroepithelial tumor (DNET) are the most common LEAT, and they will be discussed separately.

FCD Type IIIc

In FCD type IIIc, cortical dyslamination occurs near a vascular malformation such as arteriovenous malformations, cavernous hemangiomas, or telangiectasias among others (Figure 3D-3F).[20] An intact surgical resection specimen, preferably en bloc, is optimal to establish the neuropathological diagnosis; if the vascular lesion cannot be reliably characterized histopathologically, then a diagnosis of FCD type I or II may be appropriate.

FCD Type IIId

In this type of FCD, the affected patients sustained brain injuries early in life and the damaged tissue occurs near a focus of dyslaminated cortex (Figure 3G-3I).[20] The lesions encompassed by type IIId are diverse and include perinatal hypoxic-ischemic injuries and the resulting glial scarring, traumatic brain injury, and various inflammatory and infectious conditions because of autoimmune, bacterial, or viral etiologies.[43,44]

The pathogenesis of types IIIc and IIId is unknown but are likely acquired with alterations in cortical architecture arising secondary to the respective principal lesion as part of the reactive response to injury and neural plasticity.[44,45]

OTHER MCD

FCD is the most common MCD; however, others are recognized, ranging from mild to more severe conditions such as hemimegalencephaly, TSC, and polymicrogyria.[46-49] Hemimegalencephaly refers to the presence of an enlarged cerebral hemisphere and is associated with epilepsy and developmental delay. Surgery to remove or disconnect the epileptogenic focus within the offending hemisphere is often required.[50] Hemimegalencephaly can occur alone or in association with a variety of syndromes.[49] Gross examination of the cortex may show polymicrogyria, polygyria, or pachygyria, whereas cortical thickening is typically noted in cut sections (Figure 4A). Histopathology is highly variable featuring cortical dyslamination (Figure 4B) often with dysmorphic or hypertrophic neurons (Figure 4C and 4D) and increased white matter neurons, whereas gray matter heterotopia in white matter or glioneuronal leptomeningeal heterotopia are possible.

TSC is due to *TSC1* or *TSC2* germline mutations that cause inappropriate mTORC1 signaling that perturbs cell growth and differentiation.[51] Central nervous system pathology is very common, and about 80% of patients have epilepsy.[52] It is believed that medically refractory epilepsy stems from cortical tubers and resection of the tuber and adjacent cortex results in good control.[53-55] Grossly tubers are firm, and their cut surfaces have indistinct cortical white matter junctions (Figure 4E). Histopathologically, there is pronounced cortical dyslamination with dysmorphic neurons, balloon cells, and mineralization (Figure 4F-4H).[56] The balloon cells express both glial and neuronal markers, which are believed to reflect impaired cellular differentiation.[57] Of note, hemimegalencephaly, FCD type II, and TSC tubers show histopathological overlap and common genetic alterations, which suggest that they arise because of mTORopathy.[32,33,58]

Polymicrogyria may occur because of genetic or acquired processes, such as infection or hypoxic-ischemic injury. It may be focal or diffuse, involving multiple lobes, and tends to be perisylvian in location.[46,48,59] Polymicrogyria characteristically shows an excessive number of small gyri with sparse intragyral white matter that appear to pile up on each other (Figure 4I-4K).

NEOPLASMS

Although seizures may occur with any type of brain tumor, some, known as LEAT, are particularly associated with long-term medically refractory epilepsy.[41,42,60] LEAT are typically low-grade mixed neuronal and glial neocortical tumors of young patients who present with epilepsy as the main or only symptom. LEAT are slow growing with a long clinical course, which is believed to underlie the abnormalities in peritumoral neocortex that often accompanies these tumors.[61] Because ganglioglioma and DNET are the most prevalent LEATs, they will be our focus.[41,42,62]

Ganglioglioma

Gangliogliomas are the most common epilepsy-associated tumor, and seizures are their most frequent presentation. Gangliogliomas characteristically affect children or young adults with a slight male predominance and arise in the temporal (79%) and frontal lobes (12%) (Figure 5A).[62,63] Gangliogliomas are generally WHO grade I lesions that have a favorable prognosis following resection with recurrence free survival rates exceeding 90%.[63] Anaplastic transformation of a grade I ganglioglioma is a rare event.[64,65] Early surgery is associated with improved seizure control and gross total resection is recommended.[66]

Gangliogliomas have neoplastic neuronal and glial components and compact growth architecture with limited or no infiltration into adjacent tissue (Figure 5B). Lymphocytic aggregates especially around blood vessels are a common finding (Figure 5C). The neuronal component consists of large, dysmorphic neurons with perimembranous clumping of Nissl substance, distorted

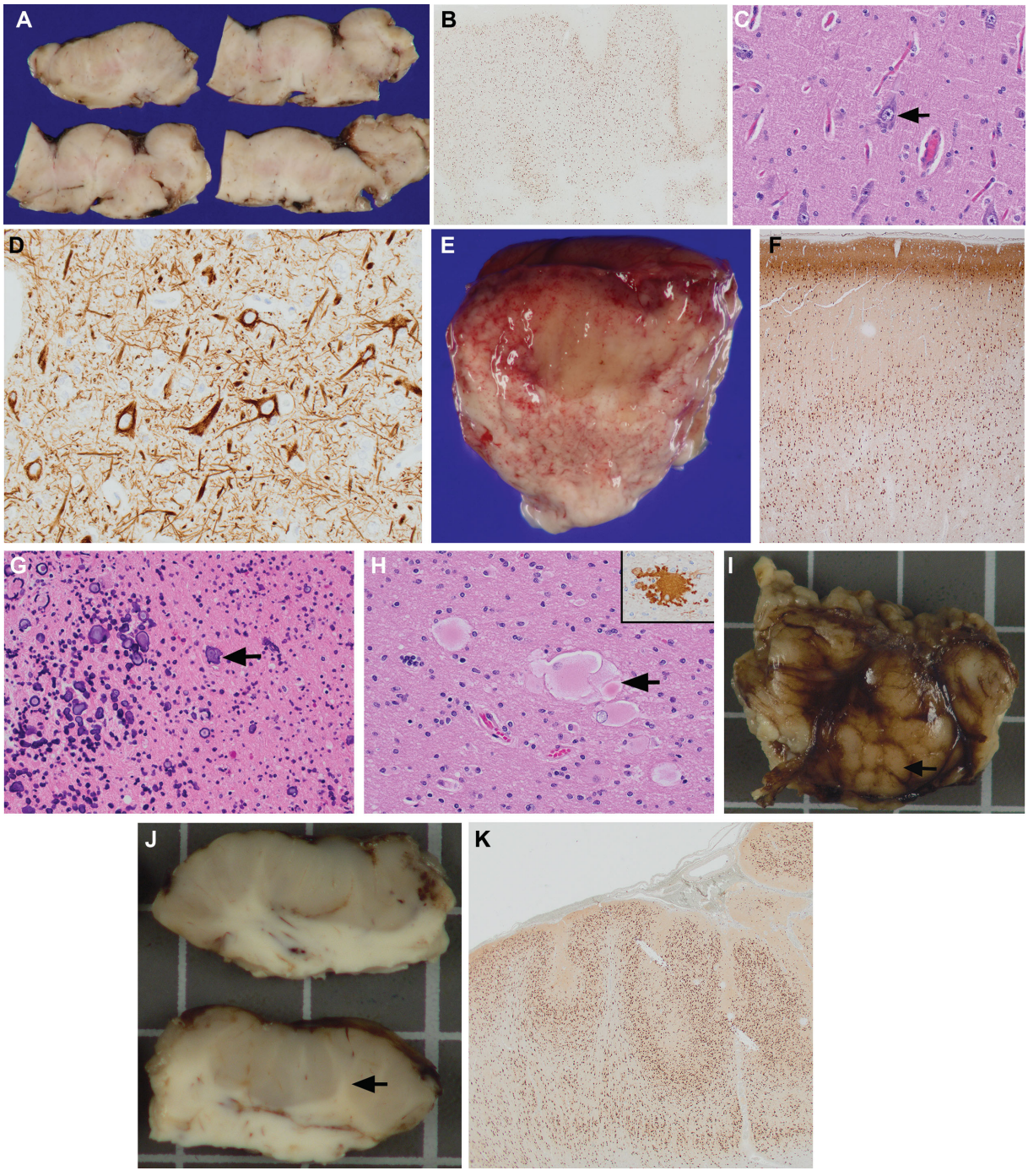

FIGURE 4. *Neuropathology of other MCDs is as follows: hemimegalencephaly* **A-D**, *TSC* **E-H**, *and polymicrogyria* **I-K**. **A**, *Cut surface of a resection specimen from a patient with hemimegalencephaly showing thickened, simplified cortex and obscure cortical white matter junctions.* **B**, *NeuN immunostain reveals haphazardly situated neurons devoid of cortical lamination.* **C**, *Hematoxylin and eosin staining showing dysmorphic neurons (arrow).* **D**, *SMI32 immunostain shows cytoplasmic accumulation of neurofilament protein.* **E**, *Resected tuber from a TSC patient showing thick cortex and indistinct cortical white matter junction.* **F**, *NeuN immunostain shows irregular neuronal layering and patchy areas with a paucity of neurons.* **G**, *Hematoxylin and eosin staining shows abundant calcification (arrow).* **H**, *Balloon cells with prominent eosinophilic cytoplasm (arrow); inset shows a balloon cell with intense vimentin immunoreactivity.* **I**, *External surface of a gross resection specimen shows many small gyri.* **J**, *Cut surface reveals numerous small gyri with thin intragyral white matter (arrow).* **K**, *NeuN immunostain reveals dyslamination.*

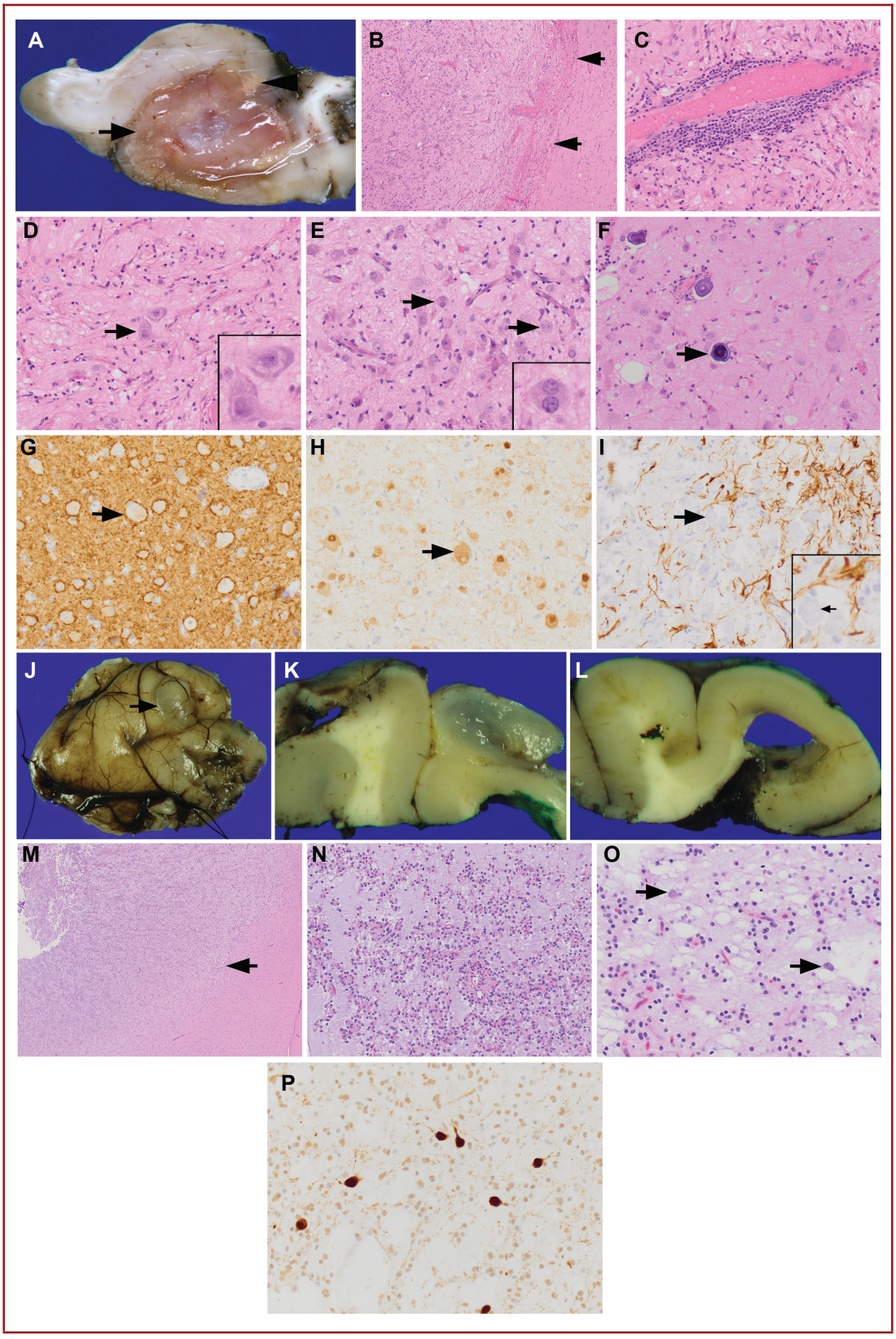

FIGURE 5. *Neuropathology of ganglioglioma* **A**-**I** *and DNET* **J**-**P**. **A**, *Coronal section of temporal lobe with hippocampus on left adjacent to ganglioglioma (arrow). The arrowhead indicates a focus of mineralization.* **B**, *Hematoxylin and eosin-stained section at low magnification shows a well-circumscribed border of tumor (arrows) with adjacent non-neoplastic brain tissue.* **C**, *Hematoxylin and eosin-stained section showing perivascular mononuclear inflammation.* **D**, *Hematoxylin and eosin showing dysmorphic neurons with clumped Nissl substance (arrow and inset).* **E**, *Hematoxylin and eosin showing binucleated neurons (arrows and inset).* **F**, *Hematoxylin and eosin showing mineralization (arrow).* **G**, *Synaptophysin immunostain labels the cell body membrane of tumor neurons.* **H**, *NeuN immunostain labels the cell body and nuclei of the neuronal component.* **I**, *GFAP immunostain highlights the glial component, whereas the neuronal component is negative (arrow and inset).* **J**, *External surface of a resection specimen with a nodular appearing DNET (arrow) within the cortex.* **K** *and* **L**, *Cut sections of DNET in* **J** *showing well-circumscribed, gelatinous appearing DNET in cortex* **K** *and loss of subcortical white matter with cystic change in an adjacent section* **L**. **M**, *Hematoxylin and eosin-stained section shows well-delineated border (arrow) of DNET (left) with adjacent non-neoplastic brain (right).* **N**, *Hematoxylin and eosin shows glioneuronal element with OLC.* **O**, *Hematoxylin and eosin staining shows glioneuronal element with neurons floating (arrows) in a myxoid matrix among OLC.* **P**, *NeuN immunostain highlights floating neurons.*

cell processes, and a vesicular nucleus with visible nucleoli (Figure 5D). Binucleation or multinucleation may be seen (Figure 5E). Calcifications and myxoid material are common findings (Figure 5F). Synaptophysin immunolabels the cell body membrane, and there is variable labeling for other neuronal markers (Figure 5G and 5H).[67] The glial component is typically astrocytic in nature (Figure 5I). Eosinophilic granular bodies or Rosenthal fibers may be encountered. Gangliogliomas, particularly those harboring *BRAF* V600E mutation, tend to have a subset of cells that immunolabel with CD34 and often cluster near dysmorphic neurons.[62,68] The glial component is the proliferative portion of the tumor, and although mitotic rates are generally low, they are increased in anaplastic ganglioglioma. Anaplastic ganglioglioma may show pleomorphism, microvascular proliferation, and necrosis. The risk of malignant progression in ganglioglioma is estimated at 3%.[41,65,69] Pediatric anaplastic ganglioglioma has a mean overall survival of 43 mo with a 45% survival rate at 3 yr.[70]

Gangliogliomas harbor genetic alterations in *BRAF*, *KRAS*, *RAF1*, *NF1*, or *FGFR1/2*, which converge onto and activate the MAP kinase pathway, whereas a subset has *CDKN2A* deletion.[71,72] *BRAF* V600E may be present, and these gangliogliomas may have a more aggressive clinical course.[73] Anaplastic ganglioglioma may have other changes such as *hTERT* promoter mutations, increased p53 expression, or loss of ATRX expression.[74] It has been suggested that DNA methylation profiling may be a more reliable method to classify gangliogliomas than histopathology alone.[41]

Dysembryoplastic Neuroepithelial Tumor

Dysembryoplastic neuroepithelial tumors are practically always associated with seizures, especially partial seizures. Seizure control is excellent following complete tumor resection, especially if the peritumoral epileptogenic tissue is also excised.[75,76] Longer duration of epilepsy and extratemporal location are associated with poorer outcome.[40,75,77] Recurrence, especially in extratemporal DNET, or regrowth following partial resection is infrequent but may occur.[78,79] DNETs are slow growing, WHO grade I tumors, yet examples with anaplastic changes and higher proliferation rates are known.[79-82] Anaplastic transformation of a grade I lesion is distinctly uncommon and believed to occur in less 1% of cases.[41,79,83-85]

The typical DNET is a cortically based, nodular, or multinodular tumor of a temporal lobe, although other lobes may be affected (Figure 5J-5M). DNETs are populated by a mix of neuroepithelial cell types including oligodendroglial-like cells (OLC), astrocytes, and neurons (Figure 5N). The defining feature is the presence of the glioneuronal element consisting of OLCs aligned in columns along capillary-sized vessels in a myxoid matrix containing what appear to be floating neurons, but this is not universally present (Figure 5O).[85] DNETs are heterogeneous architecturally with 3 forms: simple, complex, and nonspecific or diffuse. The simple and complex forms both show the glioneuronal element, whereas the complex form also has glial nodules that can morphologically resemble pilocytic astrocytoma, diffuse astrocytoma, oligodendroglioma, or ganglioglioma. The nonspecific form lacks the glioneuronal element and nodular growth pattern, and because it is histologically similar to but generally different in terms of clinical course from pilocytic astrocytoma, diffuse astrocytoma, or oligodendroglioma, this form of DNET is controversial.[86]

The OLC component typically shows more neurocytic than oligodendroglial differentiation even though neuronal markers can be weak or negative.[85,87,88] Neuronal markers, such as NeuN, will immunolabel the floating neurons of the glioneuronal element (Figure 5P). The floating neurons lack dysmorphic features encountered in ganglioglioma, so it has been suggested that they are entrapped, non-neoplastic neurons; however, this seems unlikely for DNETs arising outside of the cortex.[89,90] Molecular analysis shows that MAP kinase pathway activation and somatic or germline *FGFR1* alterations and *BRAF* V600E mutations are important pathogenetic events in DNET.[91,92]

The prognosis is generally favorable from both epilepsy and neuro-oncological perspectives if the LEAT and dysplastic perilesional cortex are resected.[40] The morphological diagnosis of the different LEAT entities can be challenging because of their diversity of growth patterns, which include nodular, cystic, or diffusely infiltrative forms and to their mixed population of glial and neuronal cells, which can make it difficult to discern tumor elements from those of the non-neoplastic brain; these

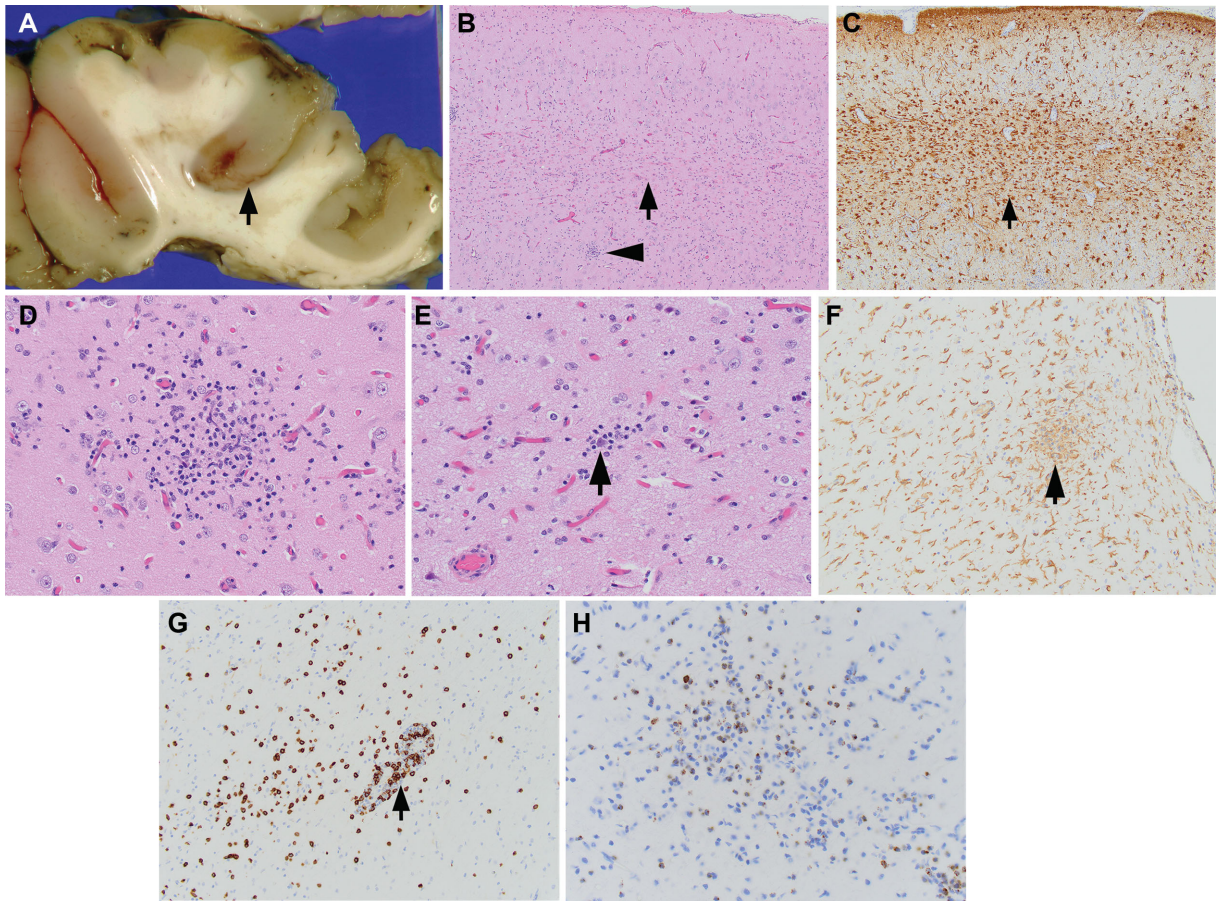

FIGURE 6. *Rasmussen encephalitis.* **A**, *Cut surface of gross resection specimen showing cleft-like lesion in cortex.* **B**, *Hematoxylin and eosin- and* **C**, *GFAP-immunostained sections highlighting laminar injury to the cortex with marked gliosis as reflected by intense GFAP immunolabeling. The arrowhead in* **B** *indicates a microglial nodule.* **D**, *High magnification of hematoxylin and eosin-stained section with a microglial nodule.* **E**, *Small microglial nodule encircling a neuron (arrow) undergoing neuronophagia.* **F**, *Iba1 immunostain highlighting a microglial nodule (arrow) and diffuse activation of microglia in brain parenchyma at a distance from the microglial nodule.* **G**, *CD8 immunostain reveals numerous cytotoxic T cells in brain tissue and around a vessel (arrow).* **H**, *Immunostain demonstrating granzyme expression in active cytotoxic T cells within brain tissue.*

factors conspire to limit diagnostic reproducibility.[41,42,93] For this reason, LEAT should be considered in all young patients with a history of epilepsy, especially those with a temporal lobe tumor.[41] Histopathology alone seems suboptimal for classification, and genomic studies have identified distinct subgroups that exhibit partial concordance with histopathology.[61,92] These findings suggest that integrating histopathological and molecular findings could enhance diagnostic accuracy.[41,61]

RASMUSSEN ENCEPHALITIS

Rasmussen encephalitis is a chronic disorder that causes medically refractory epilepsy and progressive cognitive and neurological deficits. It is likely due to a T-cell- and microglia-driven chronic inflammatory response that damages the cortex of one cerebral hemisphere. Overall Rasmussen encephalitis is a rather infrequent cause of medically refractory epilepsy with about 1 or 2 cases per 10 million people.[94,95] It mostly affects children and adolescents with no gender predilection.[96] The clinical course has been characterized, and different seizure semiologies manifest as the inflammatory process spreads within the affected hemisphere to involve new areas.[95] Most patients fail antiepileptic drug therapy and anti-inflammatory or immunomodulatory measures have had mixed success, so surgical resection or disconnection of the affected hemisphere is typically needed for epilepsy management.[97-99]

Grossly, the involved cortex is atrophic and may show small cleft-like spaces or be firm because of gliosis (Figure 6A). The cortical involvement may be laminar in distribution (Figure 6B and 6C). Histopathological features include perivascular

collections of lymphocytes, microglial nodules, neuronal loss, and neuronophagia and gliosis (Figure 6B-6F). Most of the lymphocytes are CD8 positive, and a subset will express granzyme (Figure 6G and 6H).[100] The histopathology is reminiscent of viral encephalitis, and this is part of the differential diagnosis; correlation with cerebrospinal fluid or serology testing results is warranted. Immunostains for viruses may be considered in some settings and are negative.

CONCLUSION

Our understanding of the neuropathology of epileptogenic lesions amenable to neurosurgical management has expanded considerably in recent years, and this progress will undoubtedly continue as advances in neuroimaging, neurophysiology, and genetics are used to further study these lesions. As a result, our understanding of established epileptogenic lesions will be refined, novel entities will likely emerge, and new classification systems will be formalized. It is possible that in the future genetic and morphological findings will become integrated into neuropathologic diagnostic practice as has been done for brain tumors.[41]

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